Abstract P573

# PHARMACOKINETIC EXPOSURE EQUIVALENCE AND PRELIMINARY EFFICACY AND SAFETY FROM A RANDOMIZED CROSSOVER PHASE 3 STUDY OF AN ORAL HYPOMETHYLATING AGENT, ASTX727 (DEC-C), COMPARED TO IV DECITABINE IN AML PATIENTS

Klaus Geissler[1], Zdenek Koristek[2], Teresa Bernal del Castillo[3], Jan Novák[4], Gabriela Rodriguez Macias[5], Stephan K. Metzelder[6], Arpad Illes[7], Agnes Nagy[8], Jiri Mayer9, Montserrat Arnan[10], Mary-Margaret Keating[11], Jürgen Krauter[12], Monia Lunghi[13], Nicola Stefano Fracchiolla[14], Uwe Platzbecker[15], Valeria Santini[16], Yuri Sano[17], Aram Oganesian[17], Harold Keer[17], Michael Lübbert[18]

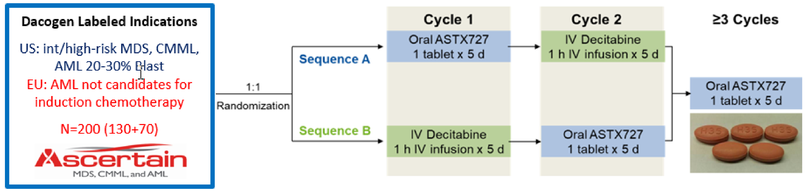
[1]Clinic Hietzing, Vienna, Austria, [2]University Hospital Ostrava, Ostrava, Czechia, [3]Hospital Universitario Central de Asturias, Oviedo, Spain, [4]Department of Haematology, 3rd Faculty of Medicine, Charles University and Faculty Hospital Kralovske Vinohrady, Prague, Czechia, [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]Philipps-Universität Marburg, Marburg, Germany, [7]Division of Haematologoy, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debreccen, [8]Department of Internal Medicine, University of Pécs, Pécs, Hungary, [9]Fakultni Nemocnice, Brno, Czechia, [10]Hematology Department, Servei d'Hematologia, Institut Català d'Oncologia, Hospital Duran i Reynals, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Universitat de Badcrcelona, L'Hospitalet de Llobregat,, Barcelona, Spain, [11]Queen Elizabeth II (QEII) Health Sciences Centre, Halifax, Nova Scotia, Canada, [12]Städtisches Klinikum Braunschweig, Braunschweig, Germany, [13]Azienda Ospedaliero-Universitaria Maggiore della Carità Novara, Novara, [14]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy, [15]University Hospital Leipzig, Leipzig, Germany, [16]MDS Unit, AOU Careggi, DMSC, University of Florence , Firenze, Italy, [17]Astex Pharmaceuticals, Inc., Pleasanton, United States of America, [18]Universitaetsklinikum Freiburg, Freiburg, Germany

## INTRODUCTION

- Cedazuridine is a novel, potent, and safe inhibitor of cytidine deaminase
- When given in combination with decitabine, cedazuridine enables efficient oral availability of decitabine
- ASTX727 (oral decitabine and cedazuridine or DEC-C) has been shown in MDS patients to produce equivalent AUC exposures to a standard 5-day regimen of IV decitabine dosed at 20 mg/m$^2$ (Savona, et al, ASH2020 Abstract 1230.)
- Here we present preliminary results using ASTX727 in an AML population


## STUDY DESIGN

### Figure 2: ASTX727-02 (ASCERTAIN) AML Cohort: Phase 3 Randomized Cross-Over Design




130 MDS/CMML patients (118 evaluable) were enrolled for the primary PK endpoint of the study. Approximately 70 AML patients were planned to be enrolled into an additional part of the study to obtain PK and efficacy data in this population.

**Major entry criteria**
- Candidates for IV decitabine
- ECOG PS 0-1
- Life expectancy of >3 months
- Adequate organ function
- One prior cycle of HMA is allowed

**Primary endpoint**
- Total 5-day decitabine AUC equivalence (Oral/IV 90% CI between 80% and 125%)

**Secondary endpoints**
- Efficacy: Response rate; duration of response; transfusion independence; event-free survival, and overall survival
- Safety of ASTX727
- Maximum LINE-1 demethylation

### Table 1: Patient Characteristics/Demographics

| Characteristics | | Total Treated N=87 |
|---|---|---|
| Median age, years (range) | | 78.0 (61–92) |
| Sex | Male | 53 (60.9%) |
| | Female | 34 (39.1%) |
| Median weight, kg (range) | | 73.7 (46.2-117.0) |
| Median BSA, m$^2$ (range) | | 1.84 (1.4 - 2.5) |
| Cytogenetic Risk Classification | Poor-Risk | 33 (37.9) |
| | Intermediate-Risk | 45 (51.7) |
| | Favorable-Risk | 0 |
| | Not Evaluable | 5 (5.7) |
| | Missing | 4 (4.6) |
| ECOG PS | 0 | 36 (41.4) |
| | 1 | 51 (58.6) |

## RESULTS

### Table 2: Primary Endpoint: 5-Day Decitabine AUC Equivalence

| Decitabine 5-day AUC$_{0\text{-}24}$ (h·ng/mL) | | IV DEC N | IV DEC Geo. LSM | Oral ASTX727 N | Oral ASTX727 Geo. LSM | Ratio of Geo. LSM Oral/IV, % (90% CI) | Intrasubject (%CV) |
|---|---|---|---|---|---|---|---|
| Primary Analysis | Paired[1] | 69 | 907.39 | 69 | 904.13 | 99.64 (91.23, 108.8) | 31.55 |

[1]Paired patient population: patients who received both ASTX727 and IV decitabine in the randomized first 2 cycles with adequate PK samples.

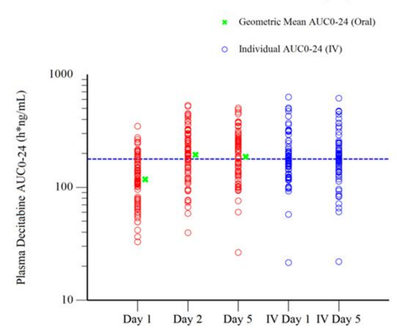
- Study met its primary endpoint with high confidence: Oral/IV 5-day decitabine AUC ~100% with 90% CI of ~91-109%
- All sensitivity and secondary PK AUC analyses confirmed findings from primary analysis

### Figure 3: Pharmacokinetics and Pharmacodynamics

| Cycle | N | Treatment | Mean Baseline | Max. *%LINE-1* Demethylation LSM | Max. *%LINE-1* Demethylation 95% CI | Difference Between ASTX727 and IV Decitabine Estimate | Difference Between ASTX727 and IV Decitabine 95% CI |
|---|---|---|---|---|---|---|---|
| 1 | 33 | ASTX727 | 75.884 | 9.357 | (7.288, 11.426) | 1.113 | (-1.698, 3.925) |
| | 39 | IV Decitabine | 76.502 | 8.243 | (6.340, 10.147) | | |
| 2 | 34 | ASTX727 | 74.764 | 8.037 | (6.258, 9.816) | -0.116 | (-2.738, 2.507) |
| | 29 | IV Decitabine | 74.640 | 8.153 | (6.226, 10.079) | | |

Results are based on an ANOVA model with treatment as factor.
ANOVA=analysis of variance; CI=confidence interval; *LINE-1*=long interspersed nucleotide element-1; LSM=least squares means

- The maximum *%LINE-1* demethylation between IV decitabine and ASTX727 (Cycle 1 and 2) was not different, with a 95% CI that included 0, consistent with both treatments producing similar PD effects.




- Individual and geometric mean plasma decitabine AUC$_{0\text{-}24}$ following daily oral administration of ASTX727 and following daily infusion of IV decitabine 20 mg/m$^2$ (semi-log scale)
- LINE-1 analyses of global methylation changes showed similar effects of IV decitabine and ASTX727

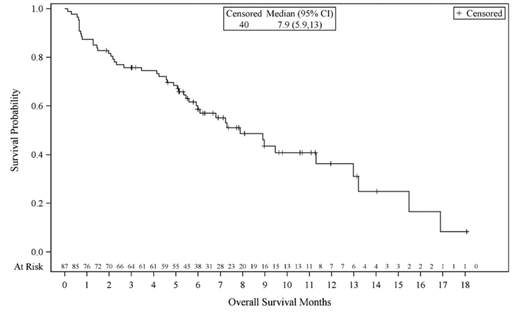
### Table 3: Preliminary Efficacy Response (ITT)

| Response category | All Treated Subjects (N=87) n (%) | 95% CI |
|---|---|---|
| Complete response (CR) | 19 (21.8) | (13.7, 32.0) |
| CR with incomplete blood count recovery (CRi) | 5 (5.7) | (1.9, 12.9) |
| CR with incomplete platelet recovery (CRp) | 2 (2.3) | (0.3, 8.1) |
| Partial response (PR) | 4 (4.6) | (1.3, 11.4) |
| Stable disease | 33 (37.9) | (27.7, 49.0) |
| Not Evaluable (NE)* | 26 (29.9) | (20.5, 40.6) |
| Composite Response (CR + CRi + PR) | 28 (32.2) | (22.6, 43.1) |

* Subjects who did not have a valid post-treatment efficacy assessment (ie, no post-treatment BM/PB sample or the quality of BM/PB sample was not adequate for an assessment of efficacy) were classified as NE for response classification.

- Median CR duration was 5.8 months
- Median time to best response was 3.4 months
- 38% of the 37 subjects who were RBC transfusion dependent at baseline were RBC transfusion independent for any consecutive ≥56-day period post-baseline

### Figure 4: Kaplan-Meier Plot of Overall Survival




- Median follow up was 7.95 months (min, max: 4.5, 19.9 months).
- mOS was 7.9 months (95% CI: 5.9, 13.0).
- 47 subjects (54.0%) had reached the event of death as of the data cutoff date (10 September 2021) and patients will continue to be followed

### Table 4: Safety: Treatment-Emergent Adverse Events in >5% of Patients*

| Preferred Term | Phase 3 Total (N=87, n[%]) | Phase 3 Total Grade 3 or higher |
|---|---|---|
| Thrombocytopenia | 22 (25.3) | 20 (23.0) |
| Neutropenia | 14 (16.1) | 14 (16.1) |
| Anemia | 14 (16.1) | 12 (13.8) |
| Febrile neutropenia | 10 (11.5) | 10 (11.5) |
| Nausea | 9 (10.3) | 0 |
| Constipation | 6 (6.9) | 0 |
| Asthenia | 6 (6.9) | 4 (4.6) |
| Decreased Appetite | 6 (6.9) | 0 |
| Diarrhea | 5 (5.7) | 0 |

*Events attributed to oral decitabine/cedazuridine

- Safety profile consistent with that of decitabine
- Most grade 3 or higher events related to myelosuppression
- GI system adverse events following ASTX727 were generally grade 1-2

## CONCLUSIONS

- In a population of AML patients not suitable for intensive induction chemotherapy, ASTX727 (oral decitabine and cedazuridine or DEC-C):
  - PK AUC equivalence to IV decitabine given at 20 mg/m$^2$ for 5-days
  - Similar pharmacodynamic activity
- With 7.95 months median follow up, results show:
  - Median Overall Survival was 7.9 months (95% CI: 5.9, 13.0)
  - CR rate is 21.8% and Composite Response (CR + CRi + PR) is 32.2%
  - No new noteworthy safety signals have emerged
- In AML patients, oral decitabine/cedazuridine (35mg /100mg) has the potential to be an oral alternative to the standard IV decitabine Daily×5 regimen
- Oral decitabine/cedazuridine is being studied in combination with venetoclax in AML patients not suitable for intensive induction chemotherapy and in MDS patients (e.g. NCT04657081, NCT04655755, NCT04746235)

## ACKNOWLEDGEMENTS

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